Growth and Death" and made them the basis of a book published the following year. For him, the subject meant cell metamorphosis, with which he had been familiar through all his studies in histology and embryology, but what he sought in this subject of "Age, Growth and Death" was a scientific solution of the problem of old age which should have—I quote his words—"in our minds, the character of a safe, sound and trustworthy biological conclusion." He ventured to think that some contemporary students of the phenomena of longevity had failed to exercise sufficient caution in forming their conclusions. Nevertheless, Minot was a scientific optimist; full of hope for perpetual progress and for useful results at many stages of the long way. These characteristics appeared clearly in the following passage, taken from the first lecture of that course at the Lowell Institute:

> I hope before I finish to convince you that we are already able to establish certain significant generalizations as to what is essential in the change from youth to old age, and that in consequence of these generalizations now possible to us new problems present themselves to our minds, which we hope really to be able to solve, and that in the solving of them we shall gain a sort of knowledge which is likely to be not only highly interesting to the scientific biologist, but also to prove in the end of great practical value.

There spoke the cautious, modest, hopeful scientist, expectant of good. Such is the faith which inspires the devoted lives of scientific inquirers.

Charles W. Eliot

THE STIMULATION OF GROWTH[1]

I

The growth of living organisms differs from that of crystals in three essential features. While the crystal grows only in a supersaturated solution of its own substance, living organisms can grow indefinitely in even a very low concentration of their nutritive solution; second, the nutritive solution need not and perhaps should not contain the compounds found in the cells, but only their split products, while in the case of the crystal the substance of crystal and solute must be identical. And thirdly, growth leads in living cells to the process of cell division as soon as the mass of the cell reaches a certain limit. Needless to say this process of cell division can not even metaphorically be claimed to exist in a crystal.

The fact that the cell can grow in a very low concentration of its nutritive solution, and the further fact that the nutritive solution only needs to contain the building stones for the complicated compounds of the cell, find their explanation in the assumption of the existence of synthetic enzymes or synthetic mechanisms in the cell.

The problem of growth is linked with that of death and immortality, since it would follow from our definition that the growth of a cell should go on eternally in a proper nutritive solution and under suitable conditions of temperature, provided that the synthetic catalyzers last and that they synthetize their own substance.[2] This is apparently true for bacteria and perhaps also for protozoa. Weismann has claimed immortality for all unicellular organisms and for the sex cells of metazoa, while he concedes mortality to the body cells. Leo Loeb recognized that immortality may be claimed also for the cells of malignant tumors, like cancer, for he had found that when he transplanted cancer cells on other animals the cells of the original cancer and

[1] Read at the meeting of the National Academy in Washington, April 19, 1915.

[2] This latter assumption leads to the connection of the problem of growth with that of autocatalysis as suggested first by the writer in 1906 and worked out subsequently in the papers of Wo. Ostwald and T. B. Robertson.

not the cells of the host grow into a new cancer. He suggested in 1901 that this claim might be extended to somatic cells in general.

> The idea suggests itself that not only the germ cells can be immortal, but that perhaps also the somatic cells, like connective tissue cells, might, under certain conditions, live for a long period, much longer than the individual life of the organism of which they were a part, that they might perhaps also be immortal in the same sense as the ovum is.[3]

Returning to the same problem in 1907 he added the following remarks:

> There exists another very striking phenomenon in the growth of malignant tumors, to which I called attention in my first communications on the transplantation of tumors, namely the fact that tumor cells have apparently an unlimited existence and that they seem to resemble in this respect the germ cells. It is certain that their life and growth exceeds that of the other somatic cells of the individual, from which they are taken. But at present we are not yet justified in saying that the tumor cells differ in this specifically from certain other somatic cells. It has been tacitly assumed thus far that the somatic cells of the metazoa have only a limited existence, but no attempt has been made to determine exactly the possible duration of life of somatic cells. We must therefore consider the possibility that certain somatic cells possess the same apparently unlimited duration of life as somatic tumor cells. . . . This seems to be a biological problem of great bearing to which the experimental investigation of tumors has led, and it might be possible to decide experimentally whether or not other cells resemble tumor cells in this respect.[4]

The experimental decision seems to have been furnished, since Carrel has succeeded in keeping connective tissue cells from a chick embryo alive for over three years, and these cells are still growing and dividing. It should be added, however, that similar attempts with other cells have not yet met with the same success.

[3] Leo Loeb, "On Transplantation of Tumors," *Jour. Med. Res.*, VI., 28, 1901.

[4] Leo Loeb, "Beiträge zur Analyse des Gewebewachstums," *Arch. f. Entwicklungsmech.*, XXIV., 655, 1907.

While thus theory and experience seem to agree to some extent, a closer examination of actual conditions reveals a somewhat different and more complicated situation. The egg cell, for which Weismann claimed immortality, can not grow and develop and will die quickly if it is not fertilized at a certain stage of its existence. The cells in the body will not grow constantly as our definition seems to demand, but their growth is followed by a period of rest from which they may be aroused by special substances or by a wound. Moreover, all differentiation of form in animals and plants depends on the fact that the different parts grow with different velocities, since otherwise all organisms would be perfect spheres.

In reality then the resting condition of a cell seems to be as much a part of real life as growth and cell division. Yet the definition from which we started is apparently correct, and it may be that we have to define the additional conditions which make a resting cell possible and which will wake a resting cell from its slumber.

II

In the usual treatment of the problem of growth the increase of mass of the whole organism is taken into consideration. While this method is adequate for the study of the relation of nutrition to growth, it is not adequate for the study of the stimulation of growth. In the latter case we must remember that it is the individual cell which grows, and that we must therefore study the mechanism of this stimulation in the individual cell and not in the organism as a whole. The ideal object for this study is the egg cell, since we can observe it in the condition of rest as well as of cell division and growth.

Since usually cell division follows growth and is possibly a consequence of the increase of mass of the cell, this rule does not

always hold in the egg cell, where as a rule immediately after fertilization a series of cell divisions follow without any increase of mass of the egg. The egg, when divided into two or more cells, does, as a rule, not weigh more (and may possibly weigh a little less) than the original egg cell before it began to divide. This exception from the rule that cell division is preceded by growth of the cell is not real, since the egg cell is at first much larger than the ordinary body cell of the growing organism. If the relation between size of cell and cell division exists we must expect that the egg cell after it is fertilized must first undergo a series of cell divisions without any growth, until each cell of the original egg has been reduced to the size of the cell characteristic for the species. Only after this has happened can the ordinary cycle of growth of the cell with subsequent cell division begin.

The writer is suspicious that even in eggs where we notice at first cell division without growth, in reality growth may take place. Such eggs as those of the sea urchin consist largely of reserve material which is gradually transformed into the peculiar state which we designate as living protoplasm (and which may differ from nonprotoplasmic material in the possession of synthesizing enzymes or mechanisms). In the first stages of cell division this transformation of reserve material into living material may occur, and this transformation is the real growth which we observe in the bacteria and later on in the cells of metazoa, but which is not directly visible in the first stages of cell division in the egg.

The unfertilized egg immediately before fertilization is usually unable to divide even under the most perfect conditions. With all the food existing in a hen's egg the germ can not grow unless it is fertilized, while this growth takes place after a spermatozoon has entered the egg. There exists, therefore, a mechanism by which the same egg cell can be in a state of rest in which growth is inhibited. What is the nature of this peculiar inhibitory mechanism and what is the mechanism by which the entrance of a spermatozoon abolishes this inhibition? The experiments on artificial parthenogenesis[5] allow us to give a partial answer to this question.

In the case of certain eggs, *e. g.*, the egg of the sea urchin, the entrance of a spermatozoon is followed immediately by a striking change in the surface of the egg. The latter surrounds itself with the so-called fertilization membrane. If we induce this membrane formation by certain chemicals (*e. g.*, a short treatment with a fatty acid) the eggs when put back into normal sea water will begin to develop at a low temperature and may reach the larval stage. But at the temperature of the room or even of the ocean the eggs may begin to develop, but they will perish the more rapidly the higher the temperature. On the other hand, the eggs if fertilized with sperm will develop at room temperature. What causes this difference? The answer is that the alteration of the surface of the egg induced by a fatty acid initiates development but is not sufficient to guarantee a normal development at ordinary conditions. For this purpose a second treatment is required and this can be given in the form of a short treatment with a hypertonic solution or a longer treatment with lack of oxygen. After the egg has received the second treatment it can develop into a normal larva at room temperature. I am suspicious that even a third factor may have to be supplied, since the mortality of the parthenogenetic larvæ is greater than that of the normally fertilized eggs.

Why is it that the membrane formation, or more correctly an alteration of the sur-

[5] The reader is referred to the writer's book on "Artificial Parthenogenesis and Fertilization," Chicago, 1913, for details and literature.

face layer of the egg, which may or may not result in a membrane formation, starts the development of the egg? The writer had found that the fertilized egg can not develop if deprived of oxygen, but that development begins again instantly if oxygen is admitted. From this and other observations he concluded that fertilization by sperm as well as artificial membrane formation induced development by raising the rate of the oxidations in the egg, and this surmise was confirmed by actual measurements by O. Warburg as well as by Wasteneys and the writer.[6] It was found that the entrance of a spermatozoon into the egg raises the rate of oxidations from 400 per cent. (*Arbacia*) to 600 per cent. (*Strongylocentrotus purpuratus*) and that artificial membrane formation by butyric acid raises the rate of oxidations to exactly the same amount.

The changes which determine this characteristic rise in the rate of oxidations of the egg are situated at the surface of the egg, in its cortical layer. The process underlying membrane formation can be called forth by any substance which causes cytolysis—that form of destruction of the cell which results in the transformation of a cell into a mere shadowy skeleton. Any cytolytic agent will induce membrane formation and also development in the unfertilized egg, if it is allowed to act on the superficial layer of the egg only, *i. e.*, if the egg is removed from its influence after the membrane formation. If it is not removed the whole egg will undergo cytolysis and can no longer develop. But such eggs will still show the rise in the rate of oxidations which follows artificial membrane formation, thus indicating that the sudden rise in the rate of oxidations which we notice after artificial membrane formation depends only upon the alteration of the surface of the egg, regardless of the condition of the rest of the egg.

The forces which induce the egg cell to develop are, therefore, localized at the surface of the cell and consist in a change (possibly a cytolysis) of the cortical layer of the egg. We do not know how this change induces the rise in the rate of oxidations upon which development depends, but from Warburg's work it appears probable that the oxidations in the sea urchin egg are due to a catalysis by iron. This would indicate the possibility that in the cytolysis of the cortical layer of the egg the iron would be transformed from a condition where it is unable to act as a catalyzer into a condition where it can act in this capacity.

We have mentioned the fact that all cytolytic agencies call forth the membrane formation in the unfertilized egg. Such cytolytic substances (the lysins of the bacteriologist) are also contained in the blood and cell extract of each animal; only with this limitation that the cells of our own body are immune against the action of our own lysins, but not against the lysins in the blood and cell extract of other animals. I was able to show that we can call forth membrane formation and development in the sea urchin egg with foreign blood, *e. g.*, ox blood, or with the extracts of foreign tissues, but not with their own blood or tissue extract. Wasteneys and the writer could show later that this method can be applied generally for artificial parthenogenesis. This immunity of the egg towards the lysins of its own body we may explain on the assumption that the lysins contained in foreign blood can enter the cell, while the latter is impermeable for the lysins contained in the blood or tissue extract of the same species. If it were not for this immunity, all the eggs would be induced to

[6] There are indications that other processes are also initiated or accelerated by fertilization, but this may be omitted from consideration in this connection.

develop before they leave the ovary. This is not the case.

The work on physiologically balanced salt solutions has brought out the fact that the permeability of the cells in a body may undergo variations and when this happens it is conceivable that the lysins in the blood may induce eggs to develop in the ovary. Leo Loeb states that 10 per cent. of the eggs in the ovary of a guinea-pig may show a beginning of parthenogenetic development, and certain spontaneous tumor formations in the human ovary may find their explanation in this way. In other words, it is not excluded that one form of limited growth may be due to the immunity or impermeability of cells to blood of the same species.

The question then why an unfertilized egg can not grow and why a fertilized egg possesses the power of dividing and growing is therefore answered in the sense that both conditions depend apparently upon the condition of the surface layer of the cell.

The most important fact for our present problem is the observation that the alteration which starts the development of the egg is to some extent reversible. The history of the egg is such that after a number of cell divisions the final stage of the unfertilized egg ready for fertilization is reached. If at that stage it is fertilized by sperm or induced to develop by artificial means the processes of cell division and growth will continue; if not, the egg will soon die. There is a third possibility. The unfertilized egg may start to develop, then stop and go practically, though not entirely, back into the state in which it was before starting to develop.

The clearest case of this kind was observed in the egg of the Californian sea urchin. When the unfertilized egg of *Strongylocentrotus purpuratus* is treated with a hypertonic solution the eggs may begin to segment into two, four, or eight or sixteen cells, but then they cease developing and go back into the resting condition in which they were before the egg started dividing, with the exception of one condition which will be mentioned later. In the place of each of the original eggs we have now two, four, eight, etc., smaller cells. The observation is of importance for the theory of fertilization, because it disposes of the idea once held by Boveri that eggs are in the resting stage because they are lacking the apparatus for cell division; these eggs went into the resting stage again in spite of the fact that they possessed the apparatus for normal cell division. If the cells of such an egg are at a later time fertilized with sperm, they form a fertilization membrane and develop. They will develop also into larvæ if they only receive the butyric-acid treatment without the corrective factor. The original treatment with the hypertonic solution provided these eggs permanently with the corrective effect.

What caused these eggs which were segmenting to go back into the resting stage? I am inclined to assume that in these eggs the change in the cortical layer which started the development was gradually or suddenly reversed. We should expect this to betray itself in a lowering of the rate of oxidations. Wasteneys and I have found indeed that unfertilized eggs of *purpuratus*, which show an increase in the rate of oxidations after a treatment with a hypertonic solution, show a lower rate if examined after some time. It seems then possible that the change in the cortical layer which leads to a rise in the rate of oxidations is under certain conditions reversible.

These are not the only cases of reversion. I noticed that if the development of the eggs of *Arbacia* is induced either by a

treatment with butyric acid or by alkali, and if the eggs are afterwards prevented from developing (by putting them for a certain length of time into sea water containing NaCN) they will go back into a resting condition from which they can be aroused again by a treatment with sperm. We suspect that in this case the reversion in development is also accompanied by a reversion in the rate of oxidations.

We see then that our definition of a cell as being constantly ready to grow and segment is not strictly fulfilled even in the case of the egg cell, which, according to Weismann, we may consider as immortal. Instead we see that the egg cell can apparently alternate between a resting condition and an active condition, and that the nature of the cortical layer of the egg determines in which of the two conditions the egg exists.

From this we might conclude that our original definition, that each cell will grow and multiply eternally, may hold after all if we add the fact, that in the egg cell a variation in the nature of the cortical layer may start or inhibit cell division and growth. We may next ask: Does this addition also satisfy the facts we find in the adult body where the cells come to rest unless they are called into active growth again by a wound or by the not definitely known causes of tumor formation? Or, in other words: Is it only a change in the cortical layer which condemns the cells of the adult body to rest and those of the young body to grow?

Unfortunately, our task is not so easy. The unfertilized egg which is ready for fertilization will die comparatively rapidly, unless it is fertilized by sperm or treated by the methods of artificial parthenogenesis. We can prolong its life by suppressing its oxidations. Before the egg is mature its duration of life seems longer. If the eggs of the starfish are allowed to mature they die in a few hours if not fertilized; if they are prevented from becoming mature they live much longer. It is not known that anything similar to this exists in the somatic cells of the adult animal. Until such knowledge is acquired we must be prepared to admit that the resting cell of an adult organism is in a condition which is not comparable to that of the unfertilized egg.

III

We know that the growth of resting cells in a body may be induced if the blood contains certain substances which differ for different kinds of cells. One of the most recent and most striking observations in this direction was that of Gudernatsch, who found that in the tadpole of a frog or a toad, whose legs usually do not begin to grow until it is several months old, the legs can be induced to grow out at any time, even in very young specimens, by feeding them with the substance from thyroid glands. No other material seems to have such an effect. The thyroid contains iodine, and Morse states that if instead of the gland iodized amino-acids are fed the same result can be produced. We must draw the conclusion that the normal outgrowth of legs in a tadpole is also due to the presence in the body of substances similar to the thyroid in their action (it may possibly be thyroid substance) which is either formed in the body or taken up with the food.

That the phenomena of larval metamorphosis are independent of the influence of the central nervous system has been amply demonstrated. Thus I could show in 1896 that if we cut through the spinal cord of an amblystoma larva the metamorphosis of the body in front and behind the cut takes place simultaneously. Uhlen-

huth showed that if the eye of a salamander larva is transplanted into another larva the transplanted eye undergoes its metamorphosis into the typical eye of the adult form simultaneously with the normal eyes of the individual into which it was transplanted. These and other observations of a similar character show that substances circulating in the blood are responsible for the phenomena of growth in this case.

A very instructive observation on the rôle of internal secretion on growth was made by Leo Loeb. When the fertilized ovum comes in contact with the wall of the uterus it calls forth a growth there, namely, the formation of the maternal placenta (decidua). Leo Loeb showed that the corpus luteum of the ovary gives off a substance to the blood which alters the tissues in the uterus in such a way that any contact with any foreign body induces this deciduoma formation. The case is of interest since it indicates that the substance given off by the corpus luteum does not induce growth directly, but that it allows mechanical contact with a foreign body to induce growth, while without the intervention of the corpus luteum substance no such effect of the mechanical stimulus would be observable. The action of the substance of the corpus luteum is independent of the nervous system, since in a uterus which has been cut out and retransplanted into the animal the same phenomenon can be observed.

All these cases agree in this, that apparently specific substances induce or favor growth not in the whole body, but in special parts of the body. This recalls the idea of Sachs that there must be in each organism as many specific organ-forming substances as there are organs in the body. When this statement was made by Sachs the facts on the specific effect of internal secretion were unknown. To-day we can say that Sachs's theory is certainly supported by a stately array of facts.

There may also be substances which affect growth more generally. This is indicated in the apparent connection of acromegaly and giantism with diseases of the hypophysis and in the inhibition of longitudinal growth after extirpation of the thyroid.

We are, however, unable to answer the question as to how these substances induce the cells to grow. Are the resting cells in the body in the condition of the unfertilized egg and does the thyroid in Gudernatsch's experiment produce an alteration of the cortical layer of the cells from which the legs grow out, similar to that caused by the butyric-acid treatment of the egg? It would not be safe to make such an assumption at present, since we do not even know whether the products of internal secretion act directly on the growing cell or only in some indirect way. We only know that conditions of rest in the cells may be interrupted by the production of certain substances in the body or by their introduction in the form of food; and conversely we may suspect that the rest of the cells may have been enforced by the presence of other substances (or cells) in the blood antagonistic to the former.

The idea that the products of internal secretion or certain substances taken up in the food do not act directly upon the cells whose growth they influence, but indirectly through an alteration of metabolism, is strongly supported by the interesting observations of Geoffrey Smith. Claude Bernard and Vitzou had shown that the period of growth and moulting of the higher Crustacea is accompanied by a heaping up of glycogen in the liver and subdermal connective tissue. Smith found that during the period between two moultings when there was no growth the storage cells are seen to be filled with large and numerous

fat globules instead of with glycogen. He also found that in the *Cladocera* "the period of active growth is accompanied by glycogen—as opposed to fat—metabolism." He observed, moreover, that if *Cladocera* are crowded at a low temperature the fat metabolism (with inhibition to growth) is favored, while at high temperatures and with no crowding of individuals the glycogen metabolism is favored. In the latter case a purely parthenogenetic mode of propagation is observed, while in the former sexual reproduction takes place. The effect of crowding of individuals is apparently due to products of excretion, which then act on growth and reproduction indirectly by modifying the "glycogen metabolism" to "fat metabolism."

IV

Factors which directly inhibit growth have been discovered by Jas. B. Murphy, of the Rockefeller Institute. It was known that tissues can not be successfully transplanted into a different species. Murphy discovered that this rule does not hold for the chick embryo. Any kind of tissue, even human, will grow if transplanted to such an embryo. This growth of the transplanted tissue will stop, however, when the chick is ready to hatch, and Murphy found that this is due to the development of a certain type of cells in the chick embryo at that period, namely, the lymphocytes. Murphy found, moreover, that he could put adult mice and rats also into the condition of tolerance to foreign tissues when he destroyed their lymphocytes by an exposure to X-rays. As soon as the lymphocytes are formed again foreign tissues can not grow any longer on the animal. In this case we have a definite inhibition of growth by the action of lymphocytes which collect around the transplanted piece. It is not yet possible to state to what extent this observation on the inhibition of growth can be generalized.

We shall see later that possibly the opposite may also be true, namely, that certain cellular elements may have an accelerating effect on growth.

V

When a wound is made, cells which had been at rest may begin to grow. In many lower animal organisms and in plants whole organs may be induced to grow as a consequence of a mutilation. These phenomena are known under the name of regeneration. The name indicates the power of a living organism of restoring lost parts.

We can see from a physicochemical viewpoint why a cell should be endowed with a power of growing indefinitely, since we only need to assume the presence of suitable synthetic enzymes in the cell; but we fail to see from the same viewpoint why an organism should have the power of restoring lost parts. Weismann and others have tried to account for this power in a metaphysical way which was shown to be in conflict with the facts.

The statement that regeneration consists in the restoration of lost parts is not always the exact expression of the actual facts. In plants, *e. g.*, we notice—in the majority of cases—not a restoration of the lost parts but the outgrowth of one or more dormant buds which are often at some distance from the seat of injury. There has been some discussion whether in view of this fact we can say that regeneration exists in plants. This merely verbal difficulty disappears if we disregard the metaphysical sense of the term regeneration and realize that the essential feature of the phenomenon is the fact that if we wound living organisms, cells or anlagen which had ceased to grow suddenly begin to grow. Thus the problem of regeneration becomes a problem of

growth and the real question is: How can the process of wounding induce growth in cells which had been at rest and would probably have remained so during the whole term of life of the individual? It is not the wound in itself which induces the growth; since in plants the growth of new organs does as a rule not occur along the area of the wound, but at some distance where an old bud existed or a new one is formed. The distance of the growing or regenerating part from the wound may be quite considerable.[7]

It has been stated that the isolation of the parts is the cause of the new growth following the wound. Thus if a leaf of the tropical plant *Bryophyllum calycinum* is cut off from the plant each of the notches will give rise to a new plant when the leaf is kept in a moist atmosphere. (This is the regular way of propagating this plant.) But no such growth will occur as long as the leaf is kept in connection with the plant (and the latter is normal). Here we seem to have a clear proof of the generally accepted statement that isolation of parts leads to regeneration. The idea seems to be still further corroborated if we cut off a leaf with a piece of the main stem of the plant and suspend it in moist air. In this case no new plants will grow from the notches of the leaf. This again seemingly supports the idea that the separation of the part from the whole is the cause of growth since the leaf attached to a piece of the stem is less isolated than a leaf without any stem. Yet it can be shown that if we diminish the degree of isolation of the leaf still more by leaving it attached to a stem still possessing the opposite leaf the power of the first leaf to form new plants in its notches is enhanced again. The experiment can be made in the following way. From the same plant let be taken (1) an isolated leaf, (2) a leaf with a piece of stem, (3) a leaf with a piece of stem and the opposite leaf; let all leaves be suspended in a moist chamber with their tips submersed in water. The first and third specimen will form new plants in the submerged parts of their leaves in a comparatively short time, while the second will do so not at all or considerably later than the others.[8] Hence the experiment shows first that complete isolation induces the leaf to form new plants, that less isolation will inhibit this phenomenon, and that still less isolation will again call forth the regeneration. It is therefore plainly impossible to state that isolation is the cause of regeneration.

Those who make such a statement usually assume the existence of inhibiting influences in the plant and explain the effect of isolation on regeneration or growth on the assumption that the isolation frees the part from this inhibiting influence of the whole organism. We should be forced to assume that in the normal *Bryophyllum* there exists an inhibiting influence which prevents the buds in the notches of the leaves from growing, while when the leaf is cut off the notches are released from this inhibiting influence. To this idea we can agree, but then the question arises: What is this inhibiting influence? Thus it is a common experience that in the isolated stem of *Bryophyllum* only the apical buds will grow, while if we cut off the apical buds the next lower buds will grow out, and so on. Hence the growth of the apical buds inhibits the growth of the lower buds. Some more recent authors have suggested that a kind of nervous influence is responsible for this inhibition. But we have already mentioned a number of facts which show

[7] The process of healing, *i. e.*, of the closing of the wound, should be kept distinct from the phenomena of growth which constitute regeneration.

[8] A full account of these experiments on *Bryophyllum* will be published in the near future.

that in animals substances circulating in the blood influence growth independently of the central nervous system. In *Bryophyllum* I have recently made some experiments which seem to agree with this humoral theory of the control of growth. It can be shown in *Bryophyllum* that if a part *a* inhibits the growth in a part *b*, the presence of *b* favors growth in *a*.

We will illustrate this by two experiments. When we suspend in the moist air of a closed vessel a stem of *Bryophyllum*, whose tip, roots and leaves have been removed, only the buds in the uppermost node will grow into shoots. The growth of the apical shoots inhibits the growth of the lower buds. But if we isolate a node near the apex and suspend it in the same moist chamber, as a rule no regeneration will occur in this node; only if we leave the lower parts of the stem connected with the apical node can the latter regenerate in moist air. Hence the lower part *b*, in which regeneration is suppressed by the topmost part *a*, is necessary or helpful for the regeneration of the top *a*.

The same effect can be produced if, instead of leaving the node near the apex in connection with the lower pieces of the stem, we leave it in connection with one leaf or part of one leaf. In this case also growth of the bud will occur in the moist air. As we have already stated, the leaf is inhibited from forming new shoots in its notches through the connection with the stem. Hence the stem which inhibits the growth of shoots in the leaves is helped by the leaf in its own regeneration.

This seems to agree at first sight with the idea first suggested by Sachs that the specific shoot-forming substances do not exist in sufficient quantity in the topmost part of the stem and that they must be supplied to this piece either by a leaf or by a larger piece of stem. And on the same principle might be explained the inhibition of the top piece upon the regeneration of the lower nodes. To this assumption the simple objection is possible that a long stem contains material enough to form a dozen shoots or more, as can be shown if the stem is cut into shorter pieces. Each of the lower nodes will in this case form two new shoots. Yet the formation of two shoots at the apical node will prevent the formation of shoots at the lower nodes, although there is enough material to form shoots in every node.

It can be shown that the upper nodes if isolated will promptly form shoots if put into a thin layer of water. Hence the presence of a leaf or of the greater part of a stem enables the upper node to form shoots in moist air either by supplying it with the necessary amount of water or by establishing a flow of material. Where we have a closed circulatory system as in animals we know that the heart action can only maintain a circulation if the blood vessels are filled with blood. The writer is not sufficiently familiar with the circulation in plants, but botanists do not assume the existence of a closed circulatory system. But, however this may be, the presence of a sufficient quantity of water seems to be the prerequisite for a constant flow of substances in the conducting vessels. If we assume that the anatomy of the conducting vessels determines a flow of substances to the apex and second that the buds in that region hold *all* or practically all the formative or specific material which induces growth, the inhibition of growth in the lower buds becomes clear.

Hence we are inclined to explain both the inhibiting effect of an organ *a* upon the regeneration in *b* as well as the accelerating effect of *b* upon *a*, from the following three factors: first, the peculiarities of the anatomy of the conducting vessels in the plant;

second, the necessity of a flow for the transport of substances inducing growth; and third, the retention of these substances (even beyond need) by or near the organs which are first induced to grow or regenerate.

Such a view is supported by the older experiments of the writer on *Tubularia*. *Tubularia* is a hydroid consisting of a hollow stem attached with stolons to a solid substrate, usually piles or rocks, and bearing at its free end a polyp. Only the region behind the hydrant and the tips of the stolons show growth, the cells in the stem do not grow any more. We can, however, induce the cells in any cross section of the stem to grow into a polyp if we cut off the rest of the stem above or beneath it. How does this operation induce growth? The first idea might be that this is due to the wound; the wound, however, can only be the indirect cause, since we perceive such an outgrowth of polyps also from the tips of the uninjured stolons.

I observed that when we cut a piece *ab* from the stem and if we suspend it in sea water, both ends *a* and *b* form polyps, but that the oral end forms its polyps considerably more quickly than the aboral end; and the difference in time may be from one or two weeks to one or two days, according to the temperature and the species used for the experiment. We may, however, induce the aboral end to form its polyps just as quickly as it would form at the oral end if we prevent the formation of the oral polyp by cutting off the oxygen supply at this end. Hence the suppression of the formation of the oral polyp accelerates the formation of the aboral polyp; and, conversely, the formation of the oral polyp retards the formation of the aboral polyp. This might at first appear to be explainable on the assumption that only a limited amount of material for polyp formation was present in the stem, but this assumption is rendered untenable by the fact that if we cut the stem into a number of pieces each piece will form two polyps, the oral one always more quickly than the aboral one. This shows that the stem has material enough not for two, but, if necessary, for a dozen polyps or more. We understand the facts, however, on the assumption that the material necessary to induce the cells at the front edge to grow into a polyp collects first at this end and is held here; and that only later it can also gather at the opposite end. This is almost the same assumption as that made to explain the phenomena in *Bryophyllum*. But in the case of *Tubularia* the visible phenomena directly support our assumption. I noticed that the formation of a polyp is always preceded by a dense collection of certain pigmented cells from the entoderm which are carried like the blood corpuscles of higher animals in the fluid which circulates through the stem. These red or yellowish cells always collect first at the oral end of a piece cut out from a stem of a *Tubularia*, but if we withdraw the oxygen from this end they collect at once at the aboral end. I mentioned that the tips of stolons may grow out into polyps without a wound. Whenever this happens the formation of a polyp is preceded by a gathering of the red cells in this tip. The question then arises: Why do these red cells gather first at the oral end of a cut piece of the stem? I am not in a position to give a definite answer to this question. I suspect that phenomena of agglutination may play a rôle in this case. All I wanted to indicate was the connection which exists between the transport of special material and the localization and inducement to growth.[9]

[9] These older observations of the writer may possibly assume a greater significance in view of the work of Jas. B. Murphy concerning the rôle of lymphocytes in the prevention of the growth of

I am inclined to see another confirmation of this interpretation in a well-known observation of Morgan on the regeneration of *Planarians*. He found that if a piece be cut from the body at right angles to the longitudinal axis the head will form along the whole cut edge of the piece, while if a piece be cut out obliquely a tiny head will form in the foremost corner of the cut edge. As Bardeen suggested, this would find its explanation on the assumption that the head formation is induced by the collection of certain material which will collect along the whole front when the piece is cut out of the body at right angles, while it is bound to collect in the foremost angle when the piece is cut out obliquely.

VI

When we summarize all the facts we may state that it may be inherent in each cell to grow and divide eternally under suitable conditions; and that we can understand this condition on the simple assumption of the existence of synthetic ferments or synthetic mechanisms in each cell which are formed from the food taken up by the cells. In reality, however, things do not happen in this way in multicellular organisms, and not even in their egg cells. The unfertilized egg can in most cases not grow even under the most favorable conditions and is doomed to die in spite of its potential immortality, unless it is fertilized or treated with the methods of artificical parthenogenesis. The condition of rest or growth depends in this case apparently upon the condition of the cortical layer of the egg and the alteration in the rate of oxidations connected with this condition.

In the body, cells may be at rest or growing, and we do not know whether the conditions which determine rest are identical with those determining rest in the egg. We know, however, that specific substances circulating in the blood can induce certain resting cells in the body to grow and that these substances differ apparently for different types of cells. It may be that in the body substances antagonistic to these may enforce the inactivity of the cells.

foreign cells in a body, to which reference was made in an earlier part of this paper.

And finally we come to the conclusion that the circulation in animals or the flow of substances in plants is an important factor in the phenomena of cell rest and cell growth, inasmuch as circulation or flow determine or influence the distribution of formed cells or non-formed elements which induce or influence growth. The phenomena of regeneration seem to find to a large extent their explanation in the fact that a wound or mutilation leads to a gathering of formed or non-formed elements in spots where without the mutilation they would or could not have collected.

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ALASKA SURVEYS AND INVESTIGATIONS

The United States Geological Survey is dispatching 12 parties to Alaska to continue the systematic surveys and investigations that have been in progress for the last eighteen years. Of these parties three will be sent to southeastern Alaska, one into upper Chitina region, one to Port Valdez; two will work in the Turnagain Arm-Knik region; one will make investigations in the Yukon-Tanana region, and two in the Ruby-Kuskokwim region, and another will traverse the little-known area lying between the Ruby district and the Tanana River. One party will be engaged in general investigations in different parts of the Territory. These parties will sail from Seattle during May, so as to take full advantage of the field season. All the men needed for the work have been engaged, and the pur-